IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	CASTADO, Cindy, et al.
Filing No.	:	10/574,297
Filing Date	:	March 31, 2006
Title	:	*Pertussis Antigens and Use Thereof in Vaccination*
Grp. /A.U.	:	1645
Examiner	:	ARCHIE, Nina
Confirmation No.	:	9309
Docket No.	:	VB60452

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW - REMARKS

This request for pre-appeal review is in response to the current Final Office Action mailed 2 Mar 2010 ("the Final Office Action"). Also filed herewith are a Notice of Appeal and a Request for Pre-Appeal Brief Review. Applicants respectfully petition for a one-month Extension of Time. The Commissioner is hereby authorized to deduct the extension fee and any other fees required in association with submission of this, concurrent, and future responses from Deposit Account No. 07-1392.

Pending claims 11, 29, 32, 53, and 54 stand rejected under 35 U.S.C. § 112, first ¶, as allegedly obvious. Dependent claims 65 and 66 stand rejected as allegedly lacking written description and enablement. Because the rejection of claims 29, 32, 53, and 54 are founded on a different statutory section from the rejection of claims 65 and 66, the rejections may be considered separately.

The rejection of claims 11, 29, 32, 53, and 54 under § 103

For the reader's convenience, independent claim 11 is reproduced below.[1] The

[1] 11. An immunogenic composition comprising a polypeptide comprising:

a) an amino acid sequence sharing at least 85% identity with SEQ ID 34 or an antigenic fragment of at least 15 contiguous amino acids of SEQ ID NO:34;

b) FHA;

c) pertussis toxin; and

d) at least one different *Bordetella* antigen selected from the group consisting of:

A) at least one *Bordetella* iron acquisition protein selected from the group consisting of a polypeptide sharing at least 70% identity with SEQ ID 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, or 28, or an antigenic fragment of at least 15 contiguous amino acids from SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, or 28;

B) at least one *Bordetella* lipoprotein selected from the group consisting of a polypeptide sharing at least 70% identity with SEQ ID NO: 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, or 98 or an antigenic fragment of at least 15 contiguous amino acids from SEQ ID NO: 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, or 98;

C) at least one *Bordetella* adhesin selected from the group consisting of fimbriae 2 and/or 3 or pertactin; and

rejection is based on the combination of Novotny, Oliver, and Peetermans in view of Kinnear and Pagliaccia. The Examiner reasons that "Novotny teach an acellular pertussis vaccine comprising a combination of *Bordetella pertussis* antigens, wherein said combination consist of isolated and purified 69 kDa antigen … and isolated and purified … FHA…, wherein the 69 kDa antigen **(pertussis toxin)** and the [FHA] are present in a ratio…." See the Office Action mailed 2 Mar 2010 (O.A.), paragraph spanning page 13-14 (emphasis added).

After discussing Oliver and Peetermans, the rejection then concludes that "…it would have been obvious to use SEQ ID NO:34, FHA, pertussis toxin, and pertactin because these antigens are taught to be useful for that purpose." (In Applicants' sequence listing, SEQ ID NO:34 is the amino acid sequence of the *Bordetella* protein BrkA.) But this legal conclusion fails on at least two of the points required to support a rejection on the theory that a claimed invention is a combination of prior art elements according to known methods to yield predictable results:[2] First, the evidence of record weighs against the conclusion that the skilled person would have recognized the results of the combination were predictable. Second, the Examiner has made an erroneous finding of fact relating to Novotny.

The evidence of record includes the following. Applicants' own disclosure shows that BrkA/pertussis toxin/FHA combination can confer a level of protection that is statistically equivalent to that provided by compositions comprising pertactin or whole-cell pertussis vaccine. See Examples 12 and 13. This result would not have been predictable to the skilled person. See Poolman (2007) *Expert Rev. Vaccines* 6:47-56. Poolman discusses a limited number of efficacious *B. pertussis* proteins for use in acellular vaccine compositions and BrkA is not among them. Poolman constitutes evidence that the person of skill in the art would not reasonably expect the presently claimed BrkA-containing

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D) at least one *Bordetella* toxin/invasin or antigens involved in toxin/invasin secretion selected from the group consisting of adenylate cyclase, dermonecrotic toxin (Dnt), Type III ss or lipopolysaccharide."

[2] To reject a claim based on this rationale, the Examiner must at least articulate the following: (1) a finding that the prior art included each elementclaimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference; (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely performs the same function as it does separately; (3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

compositions to produce the observed level of protective immunity.[3]

The factual error related to Novotny is the Examiner's finding that the 69 kDa antigen is pertussis toxin. The 69 kDa antigen of Novotny **is not** pertussis toxin, it is ***pertactin***. Novotny actually teaches that the combination of ***pertactin*** (the 69 kDa antigen) and FHA is synergistic.[4] It is elemental that the *Graham* findings require a factually accurate assessment of the art. Applicants contend that the Examiner's belief that the 69 kDa protein of Novotny was pertussis toxin led to a mistaken conclusion that the person of skill in the art would have considered pertactin optional. To the contrary, Novotny supports a conclusion that pertactin is necessary for a satisfactory immune response and that the skilled person would not find the results with BrkA as a substitute for pertactin in a similarly effective acellular pertussis vaccine predictable.

Oliver does not cure the deficiencies of Novotny. The rejection alleges that "Oliver et al teach the addition of anti-BrkA antiserum to human serum neutralizes complement resistance, thus indicating the possibility of preventing infection or colonization against Bordetella pertussis…." Applicants' representative diligently reviewed Oliver but could not find a passage identifying BrkA for "preventing infection or colonization." Clarification is requested. In any case, Oliver fails to establish that the skilled person would reasonably expect that a BrkA/pertussis toxin/FHA combination would be successful, especially in view of the evidence of Poolman.

In the final rejection, the Examiner adds Peetermans for teaching "…an accellular pertussis component which typically consists of two or three antigens (i.e. detoxified PT, FHA, or 69 kDa)…wherein 69 kDa is pertactin…." See O.A., p. 15, 1st ¶. But Peetermans merely mentions the 2-component pertussis toxin/FHA vaccines discussed in Poolman. And Peetermans actually teaches combining polio or hepatitis antigens with the 2-component pertussis vaccine, not additional pertussis antigens. Neither Kinnear nor Pagliaccia cure the deficiencies of the primary references.

By itself, the factual error regarding Novotny forecloses the establishment of a prima

[3] Poolman compares two-compnent pertussis vaccine compositions to three-component vaccine compositions and concludes: "The widely used diphtheria-tetanus-acellular pertussis (DTPa)3 and -5 combinations are generally seen as the more efficacious acellular pertussis (Pa) vaccines owing to the presence of both pertussis toxin (PT) and pertactin (PRN)", p.53, 1st bullet. Poolman was considered by the Examiner as evidenced by the Form 1449 initialed 25 Feb 2009.

[4] Novotny, col. 3, lines 21-25: "There is also provided a synergistic combination comprising i) the 69 kDa antigen from B. pertussis and ii) the filamentous haemagglutinin antigen [FHA] of B. pertussis in an amount effective to induce protection in a mammal to subsequent challenge by a virulent strain of B. pertussis."

facie case under § 103. Moreover, the evidence of record weighs against the rejection. For all these reasons, Applicants request the withdrawal of the rejection of claims 11, 29, 32, 53, and 54.

The rejection of claims 65 & 66 under § 112, written description and enablement

Claim 65 recites "A vaccine comprising the immunogenic composition of claim 11" and claim 66 recites "The vaccine of claim 65 comprising an adjuvant." Applicants address the written description rejection first.

Written Description. The rejection alleges that "…the specification does not teach the protective immunoepitope(s) of a SEQ ID NO:34 so that one of skill in the art can envision which regions of the amino acid can be conservatively substituted and still retain immunogenicity and protectiveness." This statement is factually incorrect: Applicants have already drawn the Examiner's attention to such guidance within the specification, namely the predicted epitopes of SEQ ID NO:34 on page 99, Table 5 and Table 6. See the Response filed 7 Oct 2009, p. 10, first full paragraph.

Further, at the time of filing, the BrkA polypeptide had already been described in the scientific literature; much was known about its structure, including its sequence and structural regions. See the Response filed 7 Oct 2009, p. 10, second full paragraph. Given the knowledge in the art of the structure of BrkA, including which portions are located on the surface and which are embedded in the membrane, as well as the guidance provided within the specification, Applicants suggested that Example 11 of the 2008 Written Description Training Materials should be followed. Example 11 deals with a hypothetical situation in which there is an art-recognized structure-function correlation present, as here, and concludes that written description is satisfied for sequences of at least 85% identity to a disclosed species (the same degree of identity recited in Applicants' claims).

Instead of explaining the deviation from the Guidelines, the rejection relies on Greenspan (1999) *Nature Biotechnology* 7:936-937. Greenspan is not pertinent to the present inquiry for two reasons. First, Greenspan deals with the inconsistencies between two methods for structurally defining the *specific amino acids* involved in noncovalent interactions at epitope binding sites, irrelevant here because an epitopic region of a protein can be predicted without defining which specific amino acids noncovalently interact. Second, the rejection fails to explain why the skilled person would consider substituting any

of the amino acids within the predicted epitopes given the guidance in Tables 5 and 6.

Given the incorrect factual finding, the deviation from Example 11 of the Guidelines, and the weight of the evidence favoring Applicants, the rejection of claims 65-66 for allegedly lacking written description should be withdrawn.

Enablement. Applicants request reconsideration of the rejection in view of the Response filed 7 Oct 2009, in particular view of the following three bases for rejection:

1) The rejection states that the claims are not enabled because they encompass "all vaccines to an unnamed pathogen…." Even if the claim construction is accurate, it would not support an enablement rejection: there is no legal requirement that a composition claim must recite any use for the claimed composition.

2) The rejection asserts that "…the specification does not teach the protective immunopitope(s) of a SEQ ID NO:34…." This is factually incorrect given the guidance of Tables 5 and 6, as discussed elsewhere herein.

3) The rejection alleges that Examples 12 and 13 do not demonstrate that the claimed "…composition confers 'protection' against any type of infection. It merely shows that said composition reduces infection." This reasoning is flawed. The cellular pertussis vaccine, DTPw, was used as a control in the murine model discussed in Examples 12 and 13. In Example 13, DTPw protection was statistically equivalent to protection conferred by the experimental pertussis toxin/FHA/BrkA-containing composition. Were the reasoning regarding the experimental composition correct, then the same reasoning must apply to the cellular pertussis vaccine (both conferred statistically equivalent protection). This leads to the factually unsupportable conclusion that the time-tested cellular pertussis vaccine does not confer protection against *pertussis* challenge in mice.

Given these three factual or legal flaws, the rejection of claims 65-66 for allegedly lacking enablement should be withdrawn.

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